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The investigation of diabetes in people living with HIV: A Systematic Review.

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“what is already known?”

- Diabetes appears to be more common in people living with HIV (PLHIV).
- There is not an internationally agreed screening method for diabetes in PLHIV.
- Studies have suggested HbA_{1c} to be falsely low in PLHIV.

“what this study has found?”

- OGTT is the most commonly used marker of glycaemia to diagnose diabetes and HbA_{1c} to monitor diabetes.
- Not all studies follow WHO diagnostic criteria to diagnose diabetes.
- Studies suggest a discrepancy around the accuracy of HbA_{1c} in PLHIV.

“what are the clinical implications of the study?”

- Future studies are required diagnosing diabetes using WHO criteria, and providing individual participant data on HbA_{1c} and glucose, to address screening for diabetes in PLHIV.

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Abstract

Aims

HbA_{1c} is reported to underestimate glycaemia in people living with HIV (PLHIV). There is not an internationally agreed screening method for diabetes. The primary aim was to identify which tests are performed to diagnose and monitor diabetes in PLHIV. Secondary aims were to identify if prevalence or incidence of diabetes differs according to marker of glycaemia and how figures compare in PLHIV compared to people without.

Methods

Electronic databases were searched for studies investigating diabetes in PLHIV, not pregnant, aged ≥18 years. Narrative analysis and descriptive statistics were used to describe which markers of glycaemia, and their frequency, were employed in the diagnosis and monitoring of diabetes in PLHIV. Diagnostic studies provided prevalence or incidence of diabetes.

Results

Forty-five of 1028 studies were included. Oral glucose tolerance test (OGTT), fasting glucose (FG), HbA_{1c} and Fructosamine were used to investigate diabetes. Twenty-seven studies described diagnosing diabetes, 14 using OGTT, 12 FG, 7 HbA_{1c}. All 18 studies monitoring diabetes used HbA_{1c}. Prevalence ranged from 1.3-26% and incidence 2.9-12.8%. Studies using glucose and HbA_{1c} reported HbA_{1c} to diagnose fewer people with diabetes, monitoring studies found HbA_{1c} to underestimate glycaemia levels. Controlled studies demonstrate diabetes was more common in PLHIV.

Conclusion

OGTT was used most frequently to diagnose diabetes, and HbA_{1c} to monitor known diabetes. Prevalence and incidence varied depending on marker of glycaemia used. Studies reported a discrepancy in accuracy of HbA_{1c} in PLHIV, to address this, well-designed, prospective studies, providing individual-level data on HbA_{1c} levels and an additional marker of glycaemia in PLHIV are needed.

Key words

Diabetes, HIV, HbA_{1c}, OGTT, Fasting glucose, diagnosis, monitoring.

Introduction

Current HIV care has progressed from managing disease related complications to the chronic care of long term conditions, such as diabetes, hypertension and cancer. Life expectancy for people living with HIV significantly improved with the development of antiretroviral therapies (ART).(1) Following the publication of the START trial in 2015(2), The World Health Organisation (WHO) announced a “treat all” recommendation; advising ART commencement at diagnosis irrespective of CD4 count.(3)

ART is often associated with the development of diabetes, though a recent meta-analysis found insufficient evidence of cause and effect(4) with studies suggesting the development of diabetes in people living with HIV follow more traditional risk factors.(5) The prevalence figures of type 2 diabetes in people living with HIV reported in the literature is highly varied.(6) A recent study in London presents an alarming figure of approximately 1 in 3 people living with HIV having pre-diabetes or established type 2 diabetes, with the authors urging for improvements in screening for diabetes.(7)

In order to screen for diabetes, the British HIV Association (BHIVA) recommend an annual HbA_{1c} for all people living with HIV aged 40 years and over.(8) Contrasting BHIVA, the American Diabetes Association (ADA)(9,10) and European AIDS Society (EACS) do not advocate performing HbA_{1c} and suggest a fasting glucose instead. This conflicting guidance stems from a series of studies identifying HbA_{1c} to be falsely low in people living with HIV.(11–13)

The aim of this systematic review was to identify which tests are performed to both diagnose and monitor diabetes in people living with HIV aged 18 years and older, and to identify whether there is a preferred test. Secondary aims were to identify if prevalence or incidence of diabetes differs according to marker of glycaemia used and see if this differs in people living with HIV compared to people without HIV. This will provide an evidence-based summary of the literature that may guide decision making for a population with an increased risk of developing diabetes but no consensus on how to screen for diabetes.

Research Design and Methods.

This systematic review was performed in accordance with PRISMA guidelines focusing on identifying articles that specified the markers of glycaemia used to diagnose/monitor diabetes in people living with HIV. The protocol was registered with PROSPERO (registration number CRD42019135745).

Data sources and search strategy

The search strategy was initially performed in April 2019 and repeated, using the same search terms, in November 2019. The databases used were MEDLINE, Embase and Cochrane with search terms and database appropriate medical subject headings. See appendix 1 for the search terms used.

Eligibility Criteria

Studies included for the systematic review needed to meet the following criteria: primary research published from 2010 onwards, investigating diabetes in study participants that were aged >18 years with a diagnosis of HIV, and not pregnant. Studies with a control cohort without HIV were also included. The limitation for year of publication from 2010 onwards was introduced aiming to capture articles using standardised methods for measuring HbA_{1c} (the ADA introduced HbA_{1c} as screening

tool for diabetes in 2010 and WHO in 2011), with further justification that the ADA base their guidance, discouraging the use HbA_{1c} for screening diabetes in people living with HIV, on an article published in 2009(11) enabling the review to summarise studies from this date.

For those studies measuring prevalence/incidence of diabetes the article needed to specify which marker of glycaemia and diagnostic criteria were used for diabetes. Where this was unclear, or the diagnosis was based on use of diabetes medications or clinical records, the article was excluded. Studies that monitored people already diagnosed with diabetes needed to specify the marker of glycaemia used to assess diabetes control.

Single case reports, conference abstracts and review articles were excluded. Due to restricted resources, articles included were limited to those written in English. Justification for article exclusion are documented in figure 1.

Study selection

Two reviewers, HD and EY, independently screened all titles and abstracts according to the pre-specified inclusion and exclusion criteria. Full text articles were retrieved for those deemed relevant or requiring further clarification, HD and EY again reviewed independently. Any disagreement on article inclusion was discussed with AJC. Reference list of excluded articles were searched for additional articles for inclusion.

Data extraction

Data extraction was performed on a pre-designed form. Studies were separated into diagnostic studies in those without known diabetes, providing prevalence or incidence, and monitoring studies in those with previously diagnosed diabetes. Data collected included: author, year of publication, number of participants with HIV, study design, study location, mean/median age, ethnicity of participants, marker of glycaemia used. Authors were contacted where clarification of methods or additional data were needed.

Risk of Bias and Quality Assessment of Included Studies.

Studies were assessed for risk of bias using the Newcastle Ottawa score(NOS).(14) The NOS enables the assessment of the quality of data from non-randomised studies. It uses a star system judging a study from three broad perspectives: i) selection of study groups, ii) comparability of groups, iii) ascertainment of outcome of interest for cohort studies. The higher the score the higher the quality of the study, with maximum possible score of 9. A modified version, as used by Modesti et al,(15) was created for cross sectional studies in order to ensure an equivalent scoring system. HD and EY assessed included studies independently with any disagreement discussed and resolved.

Data analysis

A narrative analysis was planned. Descriptive statistics were used to describe which tests of glycaemia, and their frequency, were employed in the diagnosis and monitoring of diabetes in people living with HIV. Diagnostic studies provided study population level prevalence or incidence of diabetes. A random-effects meta-analysis was used to generate a pooled diabetes prevalence with corresponding 95% confidence intervals for each marker of glycaemia where there were sufficient studies. Stata version 15 (StataCorp, College Station, USA) was used for all analyses. Meta-analyses and pooled prevalence are only presented for markers of glycaemia where heterogeneity was sufficiently low, denoted by an I² score below 75, which was found for oral glucose tolerance test

only. Where I^2 scores were above 75, sensitivity analyses were performed using random effects meta-analysis with the Stata metaprop command. The analysis of subgroups to explain observed heterogeneity considered the following additional factors: age (< or ≥ 40), gender predominance (male versus female), country of origin (Sub-Saharan Africa versus other region), and high versus low/middle income country. These factors did not account for the observed heterogeneity. Therefore, meta-analyses were not used for other markers of glycaemia.

In order to assess if a preferred marker of glycaemia was used in the literature studies providing individualised data were analysed assessing the sensitivity and specificity of diagnosing diabetes using HbA_{1c}.

Results

The literature review found a total of 1028 articles of which 152 duplicates were removed alongside 171 published before 2010. 705 titles and abstracts were screened of which 351 failed to meet inclusion criteria. 354 full text articles were reviewed plus an extra 3 identified via reference searching totalling 357. Following full text review 309 articles were excluded. The details of study selection are illustrated in figure 1. A total of 45 studies were included for final analysis.

Quality of studies

Appendix 5 shows the quality assessment for included studies using the NOS. The median score was low at 4 (IQR 3-4) maximum available was 9. Studies scoring low were due to lack of control group and the fact that diagnosis of diabetes was based on a retrospective review of the glycaemia.

Study characteristics

From the 45 studies included, 27 studies described diagnosing diabetes with 4 reporting incidence (displayed in Appendix 2) and 23 reporting prevalence (displayed in Appendix 3) in people living with HIV. 18 studies described monitoring previously diagnosed diabetes (displayed in Appendix 4). The following study designs were included: 22 cross-sectional; 18 cohort studies; 4 retrospective chart reviews and 1 surveillance data linkage study. Thirteen of the 45 studies included a control group of people without HIV.

Almost all global regions were represented in this review with the majority conducted in the USA (20 studies) and Sub-Saharan Africa (11 studies). The average age of all participants ranged from 32-59 years.

The cut-off points to diagnose diabetes were the same in all studies: fasting glucose (FG) ≥ 7 mmol/L (≥ 126 mg/dL); HbA_{1c} ≥ 48 mmol/mol ($\geq 6.5\%$); Oral glucose tolerance test (OGTT) 0-minute glucose ≥ 7 mmol/L (≥ 126 mg/dL) and/or 120-minute glucose ≥ 11.1 mmol/L (≥ 200 mg/dL).

Markers of glycaemia used in studies to investigate diabetes.

Table 1 displays the frequency that markers of glycaemia used within the studies to investigate diabetes. OGTT is the preferred test to diagnose diabetes and HbA_{1c} is the preferred test to monitor diabetes in those with a prior diagnosis.

Studies recording prevalence of diabetes according to marker of glycaemia

Appendix 3 describes the 23 studies recording prevalence of diabetes in 30,008 people living with HIV. Six measured HbA_{1c}, 10 FG and 13 OGTT, there was a large variation in prevalence of diabetes

reported between studies. The highest prevalence of diabetes was in people living with HIV in Cameroon at 26%(16) (diagnosis based on a single fasting glucose). The lowest prevalence recorded was 1.3%(17) (diagnosis based on the 2-hour glucose value during an OGTT) in people living with HIV in the USA.

Table 2 displays the prevalence figures in studies according to marker of glycaemia.

Oral glucose tolerance test

Thirteen studies used OGTT to diagnose diabetes. The reported prevalence ranged from 1.3%-13.3%. 4/13 studies(12,17–19) specified that diagnosis derived from only the 120-minute glucose value. The remaining 9 articles used the WHO definition with 0-minute glucose and or the 120-minute value(20–28). The lowest prevalence of diabetes was reported by Kosmiski et al(17) in the USA who diagnosed diabetes only on the 120minute value. The highest prevalence reported by Idiculla et al(21) in India who used the traditional OGTT diagnostic criteria.

Meta-analysis was performed for the 9 studies using WHO definition for diabetes using OGTT, this generated a pooled prevalence of 4% (95%CI 2-5) as shown in figure 2. Heterogeneity was acceptable, with I^2 70%, but was not reduced by sensitivity analysis accounting for age, gender, economic status/country study.

HbA_{1c}

Six studies used HbA_{1c} (>48mmol/mol (6.5%)) to diagnose diabetes. The prevalence ranged from 0%-8.4%. Coelho et al(12) did not diagnose anyone with diabetes using HbA_{1c} despite FG and OGTT identifying cases of diabetes within the same population. The highest prevalence of diabetes using HbA_{1c} was 8.4% recorded by Faurholt-Jepsen et al(19) in Ethiopia in a younger population with mean age of 32.9 years.

Meta-analysis was attempted, estimating a pooled prevalence of 5% (95% CI 3-6), but heterogeneity was too high with I^2 85.3% and did not reduce with sensitivity analysis so is not described further.

Fasting glucose

Ten studies used FG to diagnose diabetes. The prevalence ranged from 3.2%-26%. The 10 studies did not follow the same diagnostic criteria using FG, 1 study used x2 FG values(S60) to diagnose diabetes, 1 used a 3-month average of values(29) and the remaining 8 used only 1 FG value.

Meta-analysis was attempted estimating a pooled prevalence of diabetes using FG in people living with HIV of 9% (95% CI 6-12). Heterogeneity was too high with I^2 90.2% that did not reduce with sensitivity analysis so is not described further.

Studies reporting prevalence of diabetes using more than one marker of glycaemia in people living with HIV.

Four studies used HbA_{1c} and glucose to diagnose diabetes. One study compared HbA_{1c} to OGTT(25), one compared HbA_{1c} to FG(29) and two studies used OGTT, FG and HbA_{1c}(12,19). Prevalence based on HbA_{1c} was lower compared to another marker of glycaemia in three of the four studies. The remaining study by Faurholt-Jepsen et al reported highest prevalence with HbA_{1c} at 8.4%, compared to 6.6% for FG and 3% for OGTT.

Incidence of diabetes according to marker of glycaemia

Four studies measured incidence of diabetes in 12,280 people living with HIV over a follow up time ranging from 1.8-5 years. Table 2 describes the individual study characteristics. Two studies used FG(30,31), one study used HbA_{1c}(32) and the other OGTT(33). Incidence of diabetes ranged from 2.9%(30) (diagnostic criteria x2 FG values) to 12.8%(33) (diagnosis based on OGTT).

Studies monitoring diabetes in participants with a known diagnosis

Eighteen studies monitored diabetes in 31,783 people living with HIV. Appendix 4 shows individual study characteristics. Seven studies included a control group of participants without HIV.

All 18 studies used HbA_{1c} as a marker of glycaemia to monitor diabetes with studies using different HbA_{1c} value thresholds to identify 'control' of diabetes, values ranged from HbA_{1c} 7-9% defining 'good/adequate/optimal' control. 12 studies provided mean/median HbA_{1c} levels on participants with HIV and type 2 diabetes with the average values ranging from 6.2-8.2%.

Studies using more than one marker of glycaemia to monitor diabetes in people living with HIV.

Six studies used fasting glucose as an additional marker of glycaemia(13,34–37) to monitor diabetes with one study(38) also using Fructosamine, five(13,34–37) included a control cohort of participants without HIV. Four of the controlled studies compared HbA_{1c} and FG values. All reported a greater discrepancy between HbA_{1c} and FG in people living with HIV compared to the control group. Khoza et al(34) found people living with HIV had a higher FG, by 4.4%, but HbA_{1c} 2.8% lower in comparison to the control group. Slama et al(13) used multivariate median regression and found at a FG of 6.9mmol/l (125mg/dL) median HbA_{1c} were 0.21% lower in HIV infected men compared to HIV uninfected men. Glesby et al(36) found women with HIV had an HbA_{1c} 1.32% lower compare to an HIV uninfected woman with the same log fasting glucose concentration. Singh et al(37) quoted HbA_{1c} to underestimate glucose by 1.5±0.2mmol/l (27±4mg/dl).

Sensitivity and specificity of HbA_{1c} to diagnose diabetes when compared to other marker of glycaemia.

Two studies provided individual participant-level data on diabetes diagnosis by marker of glycaemia.(25,29) They calculated the sensitivity of HbA_{1c} to diagnose diabetes in comparison to FG or OGTT. Both studies had a low sensitivity and high specificity for HbA_{1c} to detect diabetes based on glucose criteria; Eckhardt(29) sensitivity 40.9%, spec 97.5% against fasting glucose; Nguyen(25) sensitivity 36.8%, specificity 99.1% against OGTT.

Prevalence of diabetes in people living with HIV compared to HIV-negative control group.

Seven studies(16,18,19,23,24,39,40) included an HIV negative control group, five(16,18,19,24,39) of which reported the prevalence of diabetes to be higher in people living with HIV (see table 2). Ngatchou et al(16) presented the greatest difference in prevalence figures between people living with HIV and the control group, 26% vs 1%. People living with HIV in this study were all ART naive and diagnosis was based on a single FG value. The study was based in the Cameroon and the authors report the high prevalence of diabetes in people living with HIV to be in keeping with African ART naive individuals. Two studies report prevalence of diabetes to be higher in the control group.(23,40)

Discussion

What markers of glycaemia are used in the literature to investigate diabetes?

This systematic review identified OGTT as the most frequently used method to diagnose diabetes and HbA_{1c} the most frequently used test to monitor diabetes in people living with HIV. Of the 14 studies using OGTT to diagnose diabetes only 10 applied the WHO diagnostic criteria none of which specified if it was the 0-minute or 120-minute glucose value used to make the diagnosis. This information is important to determine underlying pathophysiology for the type of diabetes, something not understood in people living with HIV. Guidance for prevention of type 2 diabetes is derived from participants in studies with elevated 120 minute values on OGTT.(41,42) HbA_{1c} is a more convenient test to perform but cost and laboratory availability may restrict usage in lower middle income settings (LMIC). Three out of the seven studies using HbA_{1c} to diagnose diabetes in this review were based in LMIC (Sub-Saharan Africa). Two of the 18 studies monitoring diabetes were carried out in LMIC settings (South Africa and India). No study in this review used glycated albumin and only one study used Fructosamine to monitor diabetes control. Continuous glucose monitoring was used within the search terms but no studies were identified (as well as excluded studies) that investigated diabetes diagnosis or control using this method. Continuous glucose monitors (CGM) are becoming a recognised research tool with previous studies using CGM to specifically investigate HbA_{1c} discrepancy in those with liver cirrhosis(43), cystic fibrosis(44) and people of different ethnicity.(45)

What are the prevalence figures of diabetes reported in this review?

The prevalence of diabetes presented in this review is highly varied. Depending on marker of glycaemia used prevalence ranged from 1.3-26%. Current global prevalence in the general population for all types of diabetes in those aged 20-79 years is estimated at 9.3%,(46) of which 90% will have type 2 diabetes. Due to the exclusion criteria removing studies where prevalence figures included a prior diagnosis of diabetes, or diagnosis based on usage of hypoglycaemic medication, prevalence figures in this review cannot be compared to the general population. The age of study participants also reduces generalisability. The average age of participants was 32-59 years, prevalence of diabetes increases with age, with the highest incidence of type 2 diabetes between the ages 45-64 in the US.(47) There is also an imbalance in ethnicity and study location with almost half of included studies performed in the USA, and almost a quarter in SSA. Certain ethnic groups have a higher risk for diabetes with highest prevalence in people of South East Asian or African origin and prevalence of diabetes reported at 4% in LMIC and 10.4% in high-income countries.(46)

Studies reporting the higher prevalence of diabetes (Ngathou(16) 26% and Ji(48) 22.2%) used only a single FG as their diagnostic criteria which goes against WHO diagnostic criteria requiring two FG values separated in time. The lowest prevalence (Kosmiski(17) 1.3% and Faurholt-Jepsen(19) 3%) used OGTT but participants in these studies only had an OGTT performed if FG was <7mmol/l (<126mg/dl) therefore reporting only a subgroup of people.

What are the incidence figures of diabetes?

High incidence rates of diabetes were reported in this review ranging from 13-26.2/1000 person years of follow up (PYFU). It is not possible to explain the high incident rates, only four studies measured incidence and all based in different countries, using different diagnostic methods, with a wide range in population sizes (39-7177). Other studies recording an incidence rate of diabetes in people living with HIV that were not included in this review (diagnostic criteria included previous diagnosis of diabetes or usage of oral hypoglycaemic agents) range from 4.4-14.1/1000 PYFU. (49–553). An estimation of incidence of diabetes in adults aged 18 and older in the US is 6.9/1000PYFU (95% CI 5.8-8.3).(47)

Does a particular marker of glycaemia report a higher prevalence of diabetes?

It was not possible to compare the pooled prevalence according to marker of glycaemia in this review due to the heterogeneity of included studies. Only four studies measuring prevalence of diabetes used more than one marker of glycaemia to diagnose diabetes. All four show that glucose diagnoses more people compared to HbA_{1c} in people living with HIV. One study presented a higher prevalence of diabetes using HbA_{1c}, although this observation is misleading.(19) Within this cross-sectional study three markers of glycaemia diagnosed diabetes variably; HbA_{1c} 8.4%, FG 6.6%, OGTT 3% however, not all participants included in the study had the same marker of glycaemia measured. An OGTT was only performed in those with an FG <7mmol/l, explaining the lower prevalence of diabetes compared to FG or HbA_{1c}. By combining results for participants that had either a FG >7mmol/l or 2 hour OGTT >11.1mmol/l then prevalence increased to 9.6% versus 8.4% HbA_{1c}. The remaining three studies found HbA_{1c} diagnosed fewer people living with HIV with diabetes compared to a different marker of glycaemia. Coelho et al concluded HbA_{1c} underestimates glycaemia levels in people living with HIV. Eckhardt et al recommend using FG and HbA_{1c} in conjunction to screen for diabetes. Nguyen et al and Eckhardt et al suggest that an optimal cut-off for HbA_{1c} to detect diabetes in people living with HIV is 5.8%.

The included studies investigating HbA_{1c} for monitoring diabetes found HbA_{1c} to be disproportionately low in people living with HIV. This supports the observation that HbA_{1c} diagnoses fewer people with diabetes compared to glucose. Possible theories postulated for why HbA_{1c} is falsely low in people living with HIV are based around the idea of subclinical haemolysis supported by observed higher MCV values and low haptoglobin levels in people living with HIV, with alternative explanations including an association with NRTI use.(11–13,29,38)

The two studies in this review reporting individual participant data for HbA_{1c} to diagnose diabetes compared to FG/OGTT report a low sensitivity (36.8 and 40%) and high specificity (97% and 99%). Comparing these results to a non-HIV population, a large study(S54) analysing 96 population-based health examination surveys where diagnosing diabetes was defined by HbA_{1c} >6.5% calculated a pooled sensitivity of 52.8% (95% CI 51.3-54.3%) and pooled specificity of 99.74% (99.71-99.78%) compared to FG >7mmol/l. This study recommends the inclusion of FG in all studies using HbA_{1c} in order to assess how the two tests relate. This advice is supported in a recent prospective study identifying undiagnosed diabetes within the general population.(S55)

Is diabetes more common in people living with HIV?

It is widely reported that diabetes is more common in people living with HIV supported by the fact that people living with HIV are screened for diabetes from the age of 40 in the UK, at the time of HIV diagnosis in Europe and from commencement of ART in USA. It was expected this review would report a higher prevalence of diabetes in people living with HIV compared to people without HIV. Seven studies include a control cohort, of which five report prevalence of diabetes higher in people living with HIV. Of the two papers reporting a higher prevalence in the control group, one(23) in South Africa did report prevalence of diabetes was higher in people living with HIV on 2nd line ART (5.6%) compared to the control group (4.9%), suggesting an association with type of ART and duration of HIV. They also found total 'dysglycaemia' (encompassing diabetes, impaired glucose tolerance, impaired fasting glucose) was higher in the HIV cohort 28% versus 18% in controls. The other study(40) in the USA reported prevalence using OGTT at 5.4% in people living with HIV versus 8.3% in the controls group, the authors attributing prevalence of diabetes to traditional risk factors. A recent meta-analysis(S56) looked at incidence and prevalence of type 2 diabetes in people living with HIV in SSA, although reporting high heterogeneity between included studies, they did not find an association between prevalence of diabetes and HIV infection (Risk ratio = 1.61, 95% CI 0.62-4.21, p=0.39).

What are the strengths and weaknesses of this review?

The strengths of this review include a comprehensive search strategy to capture all published studies investigating diabetes as part of their protocols, although some still could have been missed. Studies included had a standardised approach in the glycaemic markers used to diagnose diabetes enabling some comparison between studies regarding prevalence/incidence of diabetes. There are some limitations to this review. The methodology of studies included was highly varied with differences in population size, study location, age and gender of participants, although accounting for these factors did not lower heterogeneity. Finally adding a limit to year of publication meant some articles investigating diabetes in people living with HIV were excluded.

Conclusion

This review reports that the most commonly used marker of glycaemia for diagnosing diabetes in people living with HIV is OGTT, and HbA_{1c} for monitoring known diabetes. Prevalence of diabetes is highly varied between studies depending on which marker of glycaemia is used. The majority of studies using fasting glucose to diagnose diabetes make a diagnosis on a single fasting sample, contrary to WHO guidance. The data from the controlled-studies suggests that diabetes is more common in people living with HIV.

The review re-enforces a discrepancy around the accuracy of HbA_{1c}, suggesting it underestimates glycaemia in people living with HIV, demonstrated in both monitoring and diagnostic studies. HbA_{1c} is currently recommended by BHIVA as an annual screening tool and this review highlights how results could be falsely reassuring. Well-designed, prospective studies, providing individual-level data on HbA_{1c} levels and an additional marker of glycaemia in people living with HIV would further address the issue surrounding accuracy of HbA_{1c} in people living with HIV.

Table 1. Frequency markers of glycaemia used in studies.

	Marker of glycaemia used			
	HbA1c	FG	OGTT	Fructosamine
Studies measuring incidence of diabetes n=4	1	2	1	0
Studies measuring prevalence of diabetes n=23	6	10	13	0
Studies monitoring diabetes n=18	18	5	0	1
<u>TOTAL</u>	25	17	14	1

Table 2. Prevalence of diabetes according to marker of glycaemia used in each study.

	Cohort people living with HIV .				Control cohort.			
Study author, year, country	Sample size (n)	HbA1c	Fasting glucose	OGTT	Sample size (n)	HbA1c	Fasting glucose	OGTT
Coelho, 2018 Portugal	220	0	3.2	5.9*	-	-	-	-
Dave, 2011 South Africa	849	-	-	2.8	-	-	-	-
Drobnik, 2017 USA	21,157	4.2	-	-	-	-	-	-
Eckhardt, 2012 USA	395	4.6	5.6	-	-	-	-	-
Faurholt-Jepsen, 2019 Ethiopia	332	8.4	6.6	3.0*	100	2	-	-
Gianotti, 2010 Italy	84	-	-	3.6	-	-	-	-
Idiculla, 2011 India	60	-	-	13.3	-	-	-	-
Ji, 2019 Germany	63	-	22.2	-	-	-	-	-
Jin, 2016 Germany	180	-	19.4	-	-	-	-	-
Kosmiski, 2011 USA	309	-	-	1.3*	187	-	-	0
Levitt, 2016 South Africa	940	-	-	3.0	880	-	-	4.9
Maganga, 2015, Tanzania	301	-	-	9.3	153	-	-	5.2
Mohammed, 2015 Ethiopia	386	-	4.7	-	-	-	-	-
Ngatchou, 2013 Cameroon	108	-	26.0	-	96	-	1	-
Nguyen, 2019 South Africa	672	1.9	-	2.8	-	-	-	-
Pinto-Neto, 2013 Brazil	486	-	5.8	-	-	-	-	-
Polsky, 2011 USA	222	-	-	5.4	155	-	-	8.3
PrayGod, 2017 Tanzania	273	-	-	1.4	-	-	-	--
Seang, 2016 USA	285	-	-	3.2*	105	-	-	0
Shankalala , 2017 Zambia	270	-	5.2	-	-	-	-	-
Shen, 2013 China	2006	-	10.5	-	-	-	-	-
Sogbanmu, 2019 South Africa	330	6.4	-	-	-	-	-	-
Tan, 2015 Canada	80	-	-	3.8	-	-	-	-

* Diagnosis of diabetes made only on 120-minutes glucose value.

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